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TO : Examiner David J. Blanchard
Examining Group 1642

FAX NO.: 571-273-8300

FROM: Leona L. Lauder

DATE : February 22, 2006

NO. OF PAGES FOLLOWING: 12

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Jan Zavada et al.

Serial No.: 09/967,237

Group Art Unit: 1642

Filed : September 27, 2001

Examiner: David J. Blanchard

For : Anti-Idiotypic Antibodies to
MN Proteins and MN
Polypeptides

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SignatureIN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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For : Anti-Idiotypic Antibodies
to MN Proteins and MN
PolypeptidesRESPONSE TO OFFICE COMMUNICATIONMAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is in response to the communication mailed from the U.S. Patent and Trademark Office (PTO) on January 23, 2006 requesting that the Applicants file a statement of the substance of the telephone interview with Primary Examiner David Blanchard and his SPE Larry Helms that occurred on January 9, 2006.

SUMMARY OF JANUARY 9 INTERVIEW

Applicants gratefully acknowledge the telephone interview granted by Examiner David Blanchard and his SPE Larry Helms on January 9, 2006 to the undersigned Attorney for the Applicants and the patent agent with whom she works, Joan Harland, Ph.D. The interview was requested to clarify points presented in Applicants' response filed on 12/5/05, in response to the last office action mailed on 9/1/05, particularly with respect to the two new 103(a) rejections.

The office action dated 9/1/05, and Applicants' response thereto, were discussed at the January 9 interview. Applicants respectfully explained that they did not fully understand the new 103(a) rejections over Oosterwijk et al. [a] (WO 88/08854) or [b] (Int'l. J. Cancer, 38: 489-494 (1986) as evidenced by Uemura et al. (Brit. J. Cancer, 81(4): 741-746 (1999) and Pastorek et al. (Oncogene, 9: 2877-2888 (1994) and in view of Raychaudhuri et al. (U.S. Patent 5,270,202), as the identical rejections were apparently made in the office action dated 4/27/05, which rejections were overcome by Applicants' response dated 6/13/05. Applicants respectfully indicated that they could not differentiate the two 103(a) rejections withdrawn by the instant office action from the two new 103(a) rejections made in sections 13 and 14 of the instant office action. Also, Applicants did not understand the reasoning provided in the office action at page 16, which read in part: "[I]t is noted

that the features upon which applicant relies (i.e., G250 monoclonal antibody) is not recited in the rejected claims."

The examiner responded that the previous 103(a) rejections (in the office action dated 4/27/05) were overcome because the methods of Oosterwijk et al. [a] and [b] did not enable the production of the G250 monoclonal antibody (Mab) that happened to be MN-specific. The examiner then distinguished the instant 103(a) rejections as generic to any anti-MN Mab, arguing that one of skill in the art would have "a reasonable expectation of success" in producing an anti-MN Mab, using the methods of Oosterwijk et al. [a] and [b], as Uemura et al. 1999 and Pastorek et al. 1994 taught that the G250 antigen was identical to the MN protein.

Applicants respectfully but most emphatically disagreed countering that Oosterwijk et al. [a] and [b] not only did not enable the production of the G250 Mab but also did not enable one of skill in the art to produce any MN-specific MAb. The Applicants explained (as will be detailed infra), that the same conventional methods of Oosterwijk et al. [a] and [b] used to produce the G250 Mab also produced at least 4 other RCC-preferential Mabs which were apparently not MN-specific,¹ as

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1. The only identifying characteristics of the other 4 Mabs of Oosterwijk et al. [a] were their immunostaining patterns, which patterns are not those for a MN-specific Mab. However, the immunostaining patterns of the G250 Mab described in Oosterwijk et al. [a] and [b] were also not those of a MN-specific Mab, as detailed in Applicants' responses. Applicants are not aware of any evidence since

reported in Oosterwijk et al. [a]. Applicants also pointed out that basically the same conventional methods used by Oosterwijk et al. [a] and [b] were used contemporaneously by a number of other laboratories, which similarly produced RCC-preferential Mabs, which according to the only identifying characteristics reported for those Mabs, that is, their immunostaining patterns, were not MN-specific, and to Applicants' knowledge, those Mabs have never since been identified as MN-specific.

Applicants further respectfully point out that MN-specific antibodies are not RCC-preferential in the sense of primarily being expressed only in RCC. MN was discovered in cervical cancer cells (HeLA cells), and has been found to be abnormally expressed in many different kind of cancers, but has not been found to be expressed in most normal tissues.

The Applicants respectfully pointed out that Uemura et al. 1999 and Pastorek et al. 1994 are not prior art references and that the application of those two articles in a 103(a) rejection constitutes impermissible hindsight. It was unknown until years after Zavada et al. discovered and identified the MN gene and protein by nucleotide and amino acid sequences, that the G250 antigen was the same as the MN protein. Oosterwijk et al. had been unable to isolate or characterize the G250 antigen until long after the earliest priority date for the instant application.

Oosterwijk et al. [a] that would indicate that said four

Applicants respectfully emphasized that the Oosterwijk et al. [a] and [b] methods to produce Mabs preferential for antigens found in renal cell carcinoma (RCC) tissue but not in normal renal tissue, did not enable the skilled artisan to determine which of any number of such antigens found in RCC cell homogenates [which "number of new antigens in RCC" was admitted by Oosterwijk et al. [b] at page 493, column 2 to be at least "relatively large"] would be the G250 antigen. In fact, the staining characteristics of the G250 Mab described in Oosterwijk et al. [a] and [b] taught away from the G250 antigen being the same as the MN protein. Oosterwijk et al. [a] and [b] did not even know whether the G250 antigen was a protein. Applicants respectfully further pointed out that according to the cited Raychaudhuri et al. reference, one of skill in the art would not know whether or not they had an anti-idiotypic antibody that mimicked the MN antigen unless they had also isolated the MN antigen itself, to test for competitive binding to an anti-MN antibody.

Oosterwijk et al. [a] and [b] would have to teach one of skill in the art to determine which of the at least "relatively large number of new antigens in [the] RCC" cell homogenates {Oosterwijk et al. [b], supra} was MN in order for the subject 103(a) rejections to have a basis. Since Oosterwijk et al. [a] and [b] did not even know if the G250 antigen were a

other RCC-preferential Mabs were MN-specific.

protein, provided no biochemical characteristics of the G250 antigen whatsoever, and reported immunostaining patterns of the G250 Mab which are not related to those for MN, Oosterwijk et al. [a] and [b] could not have taught one of skill which of the at least "relatively large number" [id.] of RCC antigens not found in normal renal tissue was the MN antigen.

For Oosterwijk et al. [a] and [b] to have *inherently* taught one of skill in the art how to prepare MN-specific Mabs, the methods of Oosterwijk et al. [a] and [b] would necessarily have had to produce MN/G250-specific monoclonal antibodies.² However, as the Applicants pointed out, many Mabs not specific to MN would be prepared by the general and conventional methods of Oosterwijk et al. [a] and [b], which did not teach how to select from such a variety of Mabs which were MN-specific, but as explained by the Applicants actually taught away from identifying MN-specific Mabs by incorrectly describing the staining characteristics of a G250-specific mab.

2. As the Federal Circuit stated: "Inherency . . . may not be established by probabilities and possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." [*In re Robertson*, 49 USPQ2d 1949 at 1951 (Fed. Cir. 1999); emphasis added.] The PTO Board of Patent Appeals and Interference pointed out in *Ex parte Levy*, 17 USPQ2d 1461 at 1464 (Bd. Pat. App. & Int'f 1990): "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." [Emphasis in original.]

Applicants respectfully highlighted evidence that one of skill in the art would not have a "reasonable expectation of success" in producing a MN-specific Mab using the methods of Oosterwijk et al. [a] and [b]. That evidence included that from Oosterwijk et al. [a] and [b] and a number of prior art references,³ provided in Applicants' last and previous responses. Those submitted prior art references showed that at least six other RCC immunology laboratories used similar methods to Oosterwijk et al. [a] and [b] which were conventional in the art [i.e., using RCC cells (or homogenates or extracts thereof) to inject mice, followed by isolation of mouse spleen cells, fusion with myeloma cells, and screening of the supernatants of the resulting hybridomas for binding to RCC cells or normal renal cells], and produced monoclonal antibodies to thirteen other RCC-specific/preferential antigens, but not apparently any monoclonal antibodies to the MN protein according to the staining characteristics of the antibodies. Oosterwijk et al. [b] supports that there are a wide variety of Mabs that stain RCC but do not stain normal kidney tissue, referring at page 493, column

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3. Klingel et al., Am. J Kidney Dis., 19(1): 22-30 (1992) (abstract); Ebert and Bander, Immunol. Ser., 53: 469-483, (1990) (abstract); Terashima et al., Nippon Hinyokika Gakkai Zasshi, 80(6):838-846, (1989) (abstract); Blouin et al., Exp. Pathol., 36(3): 147-163 (1989) (abstract); Tokuyama and Tokuyama, Hybridoma, 7(2): 155-165 (1988) (abstract); Luner et al., Cancer Res., 46(11): 5816-5820 (1986) (article enclosed with 10/17/01 IDS); Vessella et al., Cancer Res., 45(12 Pt 1): 6131-6139 (1985) (article enclosed with 10/17/01 IDS); and Schärfe et al., Eur. Urol., 11(2): 117-20 (1985) (article).120 (1985) (article).

2 to "the relatively large number of new antigens in RCC."

[Emphasis added.]

As mentioned above, Applicants explained that Oosterwijk et al. [a] produced by their conventional methods, besides the G250 Mab, four other monoclonal antibodies to RCC-preferential antigens (RC 3, RC 38, RC 69, and RC 154), apparently none of which were specific to the G250 antigen or the MN protein [see Footnote 1, supra]. Oosterwijk et al. [a] provided no direction to one of skill in the art as to how to isolate only monoclonal antibodies specific to the G250 antigen rather than to one of those at least four other antigens.

Applicants respectfully explained further that the prior art references provided relating to preparation of monoclonal antibodies to other RCC-specific/preferential antigens resulted from only a preliminary search, and that they felt rather certain that many more such prior art references could be found.

Applicants further respectfully explained that Willex, the company working with Oosterwijk et al. on the G250 Mab, had dropped their opposition to the Zavada et al. granted European patent, corresponding to the earliest U.S. priority application to the instant application, to take a license under the Zavada et al. patents/applications.

The Examiner said that he would look at the references cited and submitted with the response. The Examiner also asked

how the monoclonal antibodies to the MN protein (e.g., the M75 Mab) were made, and how that was different from how the G250 Mab of Oosterwijk et al. [a] and [b] was made. Applicants respectfully respond to the Examiner's question below.

Comparison of the Methods of Oosterwijk et al. with Those of Applicants

Conventional methods were used to produce the G250 hybridoma that secretes the G250 Mab as described in Oosterwijk et al. [a] and [b]: a mouse was immunized with cell homogenates from primary RCC lesions. The spleen cells were isolated and fused with Sp2/0 myeloma cells. Hybridomas were selected by picking up spots on a RCC coated filter and were grown in suspension. "Tissue culture medium from these clones was tested on cryostat sections of RCC lesions and normal kidney. Clones reacting with RCC and not with normal kidney tissue were subcloned and tested on other normal tissues." [Oosterwijk [a] p. 16, lines 7-11.]

As indicated in the instant application at page 71, lines 27-32, the procedure for producing the monoclonal antibody M75 and the hybridoma VU-M75 is described in WO 93/18152, which description is provided below:

BALB/C mice were immunized with MaTu-infected HeLa cells, and their spleen cells were fused with myeloma cell line NS-0. Tissue culture media from the hybridomas were screened for monoclonal antibodies, using as antigen the p58 immunoprecipitated from cell extracts of MaTu-infected HeLa with rabbit anti-MaTu

serum and protein A-Staphylococcus aureus cells (SAC) [Zavada and Zavadova, Arch. Virol., 118: 189-197 (1991)], and eluted from SDS-PAGE gels. Monoclonal antibodies were purified from TC media by affinity chromatography on protein A-Sepharose [Harlow and Lane, "Antibodies: A Laboratory Manual," Cold Spring Harbor, Cold Spring Harbor, NY (USA); 1988].

[WO 93/18152, at page 35, lines 6-17.] As indicated in Zavada et al. WO 93/18152 in the above passage, the M75 Mab was prepared by injecting mice with MaTu-infected HeLa cells, and the tissue culture media from the resulting hybridomas were screened with the specific antigen p58 eluted from SDS-PAGE gels, and not with the RCC cell homogenate-coated filters, or RCC lesions and normal kidney, of Oosterwijk et al. [a] and [b].

Methods similar to those of Oosterwijk et al. [a] and [b] were used by several other RCC laboratories. For example, in Vessella et al. 1985, [Cancer Res., 45(12 Pt 1): 6131-6139 (1985) (article enclosed with 10/17/01 IDS)], mice were immunized with RCC cell lines, fetal kidney homogenates, or RCC surgical specimen homogenates. Resulting monoclonal antibodies were tested for reactivity against established human cancer cell lines, fetal kidney cells, fetal fibroblasts and adult kidney cells in a solid phase ELISA. Each of 4 resulting RCC-reactive Mabs were titrated against a panel of 36 established human cell cultures and immunohistological binding to tumor, normal and fetal tissue sections; one of the Mabs (designated D5D) reacted with 12 of 14 RCC cell lines but "reacted with no other cancers

or normal tissues with the exception of an occasional reactivity with a Bowman's capsule." [Abstract.] Like Oosterwijk et al. [a] and [b], in Vessella et al. the mice were injected with RCC homogenates or RCC cells and the resulting hybridomas were screened with cells or tissues and not with a purified antigen.

The main difference between Oosterwijk and Vessella was that Oosterwijk screened the Mabs for specificity using RCC cell homogenate-coated filters and cryostat tissue sections of RCC lesions and normal kidney, rather than using RCC or normal kidney cells bound, fixed and freeze-dried onto ELISA plates. Those variations of Oosterwijk were obvious variations known to one of skill in the art [e.g., Sharon et al., PNAS, 76: 1420-1424 (1979)], and would not reduce the number of antigens present to a single antigen, as did the Applicants' methods.

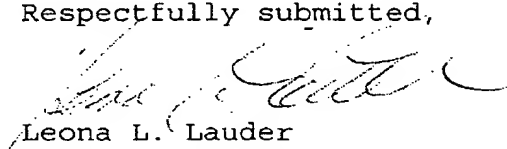
Conclusion of Interview

The Examiner said that he would carefully consider Applicants' last response and particularly look at the references submitted therewith, to determine whether the methods of Oosterwijk et al. [a] and [b] were in fact conventional in the art, and whether the methods of Oosterwijk et al. could produce antibodies, other than those specific to the MN antigen.

CONCLUSION

Applicants respectfully conclude that the subject claims are in condition for allowance, and earnestly request that the claims be promptly allowed. If for any reason the Examiner feels that a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to telephone the undersigned Attorney for Applicants at (415) 981-2034.

Respectfully submitted,



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Dated: February 23, 2006